UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	MDL Docket No. 2738
This Document Relates To All Cases	

DEFENDANTS JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER INC.'S MEMORANDUM OF LAW IN RESPONSE TO PLAINTIFFS' STEERING COMMITTEE'S OMNIBUS BRIEF REGARDING *DAUBERT* LEGAL STANDARD AND SCIENTIFIC PRINCIPLES FOR ASSESSING GENERAL CAUSATION

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Under the heading of "Omnibus Brief Regarding *Daubert* Legal Standard,"[1] plaintiffs offer the Court what is in large part a *Cliff's Notes* summary of the *Reference Manual on Scientific Evidence* – albeit one that gets a few chapters wrong. Defendants have no substantive disagreement with plaintiffs' submission to the extent it accurately summarizes the *Reference Manual*. Indeed, defendants also rely on the *Reference Manual* and agree with the clear implication of plaintiffs' brief that the *Reference Manual* should properly guide the Court's resolution of the parties' *Daubert* briefing.

In several significant respects, however, both in their Omnibus Brief and in their other *Daubert* briefs, plaintiffs depart from the well-accepted scientific principles described in the *Reference Manual* and in federal case law construing *Daubert*. Defendants therefore submit that the better approach would be to consult the *Reference Manual* and relevant caselaw rather than plaintiffs' brief for objective and accepted legal and scientific principles governing the parties' motions. In particular, defendants wish to address four central topics on which plaintiffs' Omnibus Brief and other *Daubert* briefing depart from established principles: (1) the different burdens that apply to a plaintiff's expert, who is attempting to prove a causal relationship, versus a defendant's expert, who may

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[1] (Pls.' Steering Committee's Omnibus Br. Regarding *Daubert* Legal Standard & Scientific Principles for Assessing General Causation ("Pls.' Br."), May 7, 2019 (ECF No. 9732).)

properly critique a plaintiff's expert's causation opinion without offering his or her own contrary causation opinion; (2) the proper standard governing whether an expert is qualified to provide the proffered testimony; (3) the extent of an expert's burden to review the relevant literature and what constitutes "cherry-picking"; and (4) the continued relevance of statistical significance and the hierarchy of scientific evidence.

I. DEFENDANTS' EXPERTS DO NOT HAVE A BURDEN TO DISPROVE THE ELEMENTS OF PLAINTIFFS' CLAIMS, INCLUDING CAUSATION, AND ARE INSTEAD FREE TO REST ON CRITIQUES OF PLAINTIFFS' EXPERTS' METHODS.

Plaintiffs' Omnibus Brief and several of their other *Daubert* motions suggest that the same standards apply to plaintiffs' experts, who seek to offer affirmative opinions, and defendants' experts, who seek to criticize those opinions.

This approach misapprehends the standard applicable to defendants' experts. "[D]efendants' experts have a less demanding task, since they have no burden to produce models or methods of their own; they need only attack those of plaintiffs' experts." *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 285 (E.D.N.Y. 2007). In particular, it is "entirely appropriate" for defendants' experts to offer what are, "essentially, critiques of [p]laintiffs' experts' evidence, methodologies, and conclusions." *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1368 (N.D. Fla. 2018). And "pointing to the absence of convincing studies or the weaknesses of studies on which [p]laintiffs rely, and evaluating them in light

of their . . . experience, training and research, is . . . a logical and valid approach" to responding to plaintiffs' experts' opinions. *See, e.g., In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 418-19 (S.D.N.Y. 2016).

With respect to general causation opinions in particular, court after court has similarly recognized that there "is no requirement that a defense expert offer a competing general causation opinion"; if the expert so chose, she or he could offer opinions strictly "limited to criticizing the analysis and conclusions presented by another party." *See, e.g., In re Abilify*, 299 F. Supp. 3d at 1368 (denying plaintiffs' omnibus motion to exclude various defense experts); *accord, e.g., Washington v. Kellwood Co.*, 105 F. Supp. 3d 293, 326 (S.D.N.Y. 2015) ("Defendant states—and we concur—that 'case law supports . . . that it is perfectly acceptable for an expert to critique another expert's opinion on damages without offering his or her independent opinion.'") (citation omitted). "[T]he test is different" for defense experts, as the Third Circuit explained in *Holbrook v. Lykes Brothers Steamship Co.*, 80 F.3d 777 (3d Cir. 1996), because the burden of proving causation is one that "the defense d[oes] not bear." *Id.* at 786.

For this reason, defense experts are entitled to offer opinions that would be "insufficient to prove" (or disprove) a causal relationship. *Id.*; *accord, e.g., Aycock v. R.J. Reynolds Tobacco Co.*, 769 F.3d 1063, 1069-70 (11th Cir. 2014) (district court improperly shifted the burden of proof by requiring defendants to provide

alternative theory of causation; the district court "placed the burden of proof as to causation on the wrong party"); *Wilder v. Eberhart*, 977 F.2d 673, 676 (1st Cir. 1992) (reversing exclusion of defendant's expert who failed to prove that an alternative cause was the more likely reason for the plaintiff's injury; "the defendant need not disprove causation" but need only "produce credible evidence which tends to discredit or rebut the plaintiff's evidence").

Plaintiffs' briefing reflects a failure to understand these basic principles. For example:

- A significant portion of plaintiffs' motion to exclude the testimony of Dr. Robert Kurman rests on their complaint that he "offers no causation opinions of his own" and instead provides a "general discussion of epithelial ovarian cancer and its histological subtypes" and "a critique of Dr. [Sarah] Kane's opinions";[2]
- Plaintiffs similarly attack Dr. Mary Poulton's opinions on the ground that they ostensibly "amount to nothing more than a critique of the PSC's experts rather than an expert evaluation";[3]
- Plaintiffs assert that Dr. Kelly Tuttle's biological plausibility opinions must be excluded because her opinions are based on her assessment of "other experts' work" instead of her own synthesis of "the totality of the evidence";[4] and

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[2] (Pls.' Steering Committee's Mem. of Law. in Supp. of Mot. to Exclude Ops. of Robert Kurman ("Pls.' Kurman Mot.") at 1-2, May 7, 2019 (ECF No. 9734-1).)

[3] (Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude the Geology Ops. of Drs. Mary Poulton & Laura Webb ("Pls.' Poulton & Webb Mot.") at 19, May 7, 2019 (ECF No. 9745-1).)

[4] (Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude Ops. of Defs.' Toxicology Experts Brooke T. Mossman, Kelly S. Tuttle & H. Nadia

- Plaintiffs contend that Dr. M. Darby Dyar's opinions must be excluded because, as they see it, "[t]here is no methodology in her report other than to criticize Drs. Longo and Rigler."[5]

Even if plaintiffs' characterizations of these experts' opinions were correct – and as set forth in the respective oppositions to plaintiffs' motions, they are not – the fact that a defense expert criticizes a plaintiffs' expert without attempting to proffer an affirmative opinion of his or her own is plainly no ground for exclusion under *Daubert*. Rather, as made clear in the Third Circuit's *Holbrook* decision and the many other authorities cited above, a defense expert is free to proffer alternative explanations, criticize plaintiffs' experts and identify holes in the plaintiffs' experts' evidence and reasoning without providing his or her own, affirmative opinions on general causation or any other issue. Put differently, offering scientifically-grounded criticisms of plaintiffs' experts' methods ***is*** a reliable methodology of its own, and it is plainly permissible under *Daubert*.

II. PLAINTIFFS DO NOT APPLY RULE 702'S QUALIFICATIONS REQUIREMENT EVENHANDEDLY.

Second, plaintiffs advance a double standard as to qualifications that has no support in the law. On the one hand, plaintiffs' Omnibus Brief emphasizes the

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Moore ("Pls.' Mossman, Tuttle & Moore Mot.") at 39, May 7, 2019 (ECF No. 9739-1).)

[5] (Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude Geologic Testing Ops. of Drs. Ann G. Wylie & Melinda Darby Dyar at 25, May 7, 2019 (ECF No. 9741-1).)

"liberal" nature of the qualification standard and the "minimum qualifications" needed to satisfy it, presumably in an effort to ensure that their experts are not excluded for lack of qualifications.[6] On the other hand, in their briefs aimed at defendants' experts, plaintiffs swing to the opposite end of the spectrum, advancing extreme positions about expert qualifications. For example, plaintiffs go so far as to challenge Dr. Mary Poulton's qualifications to offer geology opinions because her Ph.D. is in geological engineering and she "does not possess a geology degree."[7] They similarly challenge defendants' cancer biology experts' qualifications to offer observations about epidemiology, even though as trained medical professionals and scientists, they are required to review and understand epidemiological studies on a regular basis,[8] and even though plaintiffs' own pathologists and toxicologists purport to offer full-blown epidemiological opinions.[9]

In fact, the Third Circuit has rejected the notion that experts must always have a background in the particular "sub-specialty" about which they opine.

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6 (Pls.' Br. at 4-5.)

7 (Pls.' Poulton & Webb Mot. at 12.)

8 (Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude the Expert Ops. of Defs.' Molecular Biologists Drs. Neel, Shih, Boyd, & Birrer at 28-43, May 7, 2019 (ECF No. 9743-1).)

9 (*See, e.g.*, Expert Report of Sarah Kane, M.D. ("Kane Rep.") at 16-29, Nov. 15, 2018 (attached as Ex. C38 to the Omnibus Certification of Julie L. Tersigni ("Tersigni Cert."), May 7, 2019 (ECF No. 9723-2)).)

Schneider ex rel. Estate of Schneider v. Fried, 320 F.3d 396, 407 (3d Cir. 2003) (cardiologist of one sub-specialty could testify about standard of care for another sub-specialty; the "requirement that a witness have specialized knowledge has been interpreted liberally"); *Holbrook*, 80 F.3d at 782 (district court abused its discretion in excluding cancer opinions of doctor specializing in internal medicine); *see also Wolfe v. McNeil-PPC, Inc.*, 881 F. Supp. 2d 650, 659 (E.D. Pa. 2012) (pharmacist and toxicologist could opine on epidemiological studies even though he was not an epidemiologist); *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, Nos. 11-5304, 08-08, 2013 WL 1558690, at *6 (D.N.J. Apr. 10, 2013) (physician was qualified to opine on clinical trials even though he was not an epidemiologist). As the court in the *Avandia* litigation explained, what matters is not the title of "Epidemiologist" but rather experience reviewing and interpreting epidemiological studies in the course of the expert's professional work. *In re Avandia Mktg., Sales Practices & Prods. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *10 (E.D. Pa. Jan. 4, 2011) ("GSK does not challenge Dr. Sniderman's qualifications as a cardiologist, but does challenge his ability to analyze and draw conclusions from epidemiological research, since he is not an epidemiologist. GSK's briefs do not elaborate on this challenge, and in any event, the [c]ourt finds it unconvincing given Dr. Sniderman's credentials as a researcher

and published author, as well as clinician, and his ability to analyze the epidemiological research, as demonstrated in his report.").

Defendants reiterate their position that qualifications should not be the Court's focus at this stage of the proceedings.[10] But if plaintiffs intend to pursue their qualifications challenges, the arguments they make in their own motions would disqualify at least 14 plaintiffs' experts who have reached beyond the boundaries of their expertise, as set forth in detail in defendants' conditional qualifications motion.[11]

III. PLAINTIFFS ERRONEOUSLY CHARACTERIZE THE OMISSION OF ANY PORTION OF THE LITERATURE FROM AN EXPERT'S REVIEW AS "CHERRY-PICKING."

Although plaintiffs are correct that "cherry-picking" is an unreliable methodology,[12] they misuse the term throughout their briefing to suggest that it applies any time an expert failed to read a particular article or study that plaintiffs deem significant.

In their motion to exclude Drs. Cheryl Saenz and Kevin Holcomb, for example, plaintiffs assert that their failure to address two articles (one by Buz'Zard et al., the other by Shukla et al.), and Dr. Ghassan Saed's made-for-litigation

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10 (Defs.' Mem. of Law in Supp. of Conditional Mot. to Exclude Certain Pls.' Experts' Ops. for Lack of Qualifications at 1-3, May 7, 2019 (ECF No. 9736-6).)

11 (*See generally id.*)

12 (Pls.' Br. at 9-10 & nn.34-35.)

publication (which was not even published at the time Drs. Saenz and Holcomb issued their reports) is grounds for exclusion because it shows that they "failed to consider the totality of the evidence."[13] Plaintiffs similarly hurl allegations of cherry-picking at Dr. Nadia Moore – whose report contains hundreds of references in 454 footnotes – because she did not cite the draft report by Health Canada (which contains no new scientific data and is merely a regulatory analysis of the literature that Dr. Moore reviewed herself).[14] Plaintiffs' other briefs contain similar assertions.[15]

These accusations stretch the concept of cherry-picking too far. "Nothing in *Daubert* . . . requires an expert to consider every single article on a topic in order to be admitted as an expert." *In re C. R. Bard, Inc., Pelvic Repair Sys. Prods. Liab.*

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[13] (Pls.' Steering Committee's Mem. of Law. in Supp. of Mot. to Exclude Ops. & Test. of Defs.' Gynecology-Oncology Experts Dr. Cheryl Saenz & Dr. Kevin Holcomb at 27-28, May 7, 2019 (ECF No. 9735-1).)

[14] (Pls.' Mossman, Tuttle & Moore Mot. at 51-53.)

[15] (*See also, e.g., id.* at 27 & n.86 (similarly faulting Dr. Mossman for failing to consider Health Canada's draft assessment or the FDA's unsubstantiated claim in its response to citizens' petitions in 2014 that talc can migrate); Pls.' Kurman Mot. at 6-8 (accusing Dr. Kurman of cherry-picking based on list of eight publications, including Health Canada's draft assessment, that he did not consider); Pls.' Poulton & Webb Mot. at 22-25, 42-46 & n.97 (accusing Drs. Poulton and Webb of cherry-picking from the literature but identifying only five specific publications they claim Dr. Poulton should have considered and no specific publications Dr. Webb should have considered).) With respect to geology issues, plaintiffs interweave assertions that, beyond literature, defendants' experts also should have considered more internal company documents, but as courts have recognized, consideration of a defendant's statements in company documents is not an essential component of a reliable expert analysis. *See, e.g., In re Mirena*, 169 F. Supp. 3d at 419, 426-27.

Litig., MDL No. 2187, 2018 WL 4220616, at *5 (S.D. W. Va. Sept. 5, 2018) (expert's alleged failure to consider a "handful of articles" was not unreliable). Rather, in determining whether an expert engaged in cherry-picking, courts consider whether the expert's choice of literature was systematic and slanted – e.g., whether there is evidence that the "search of the scientific literature was in any other way infirm." *In re Abilify*, 299 F. Supp. 3d at 1341. In particular, courts look for evidence that the expert "manufacture[d] a desired result" and lacks a "reasonable, scientific explanation why he relied on some studies . . . and discounted other studies." *In re Horizon Organic Milk Plus DHA Omega-3 Mktg. & Sales Practice Litig.*, No. 12-MD-02324, 2014 WL 1669930, at *8 (S.D. Fla. Apr. 28, 2014); *see also, e.g.*, *In re Depakote*, No. 14-CV-847-NJR-SCW, 2015 WL 4775868, at *4 (S.D. Ill. Feb. 13, 2015) (rejecting argument that expert "cherry-picked" literature and noting the difference between "selectively cho[osing] *facts*" and "selective choice of *articles* and *studies*, to which [an expert] is entitled to give different weight based on design of the study, the quality of the study, the authors of the article, etc.").

As elaborated in defendants' motion-specific opposition briefs submitted herewith, defendants' experts have not engaged in cherry-picking because there has been no systematic effort to limit consideration of literature or other evidence to what is favorable to defendants' positions or the experts' conclusions. Rather,

across the board, defendants' experts identify the literature and evidence touted by plaintiffs and their experts and explain why it is not supportive of causation in light of the totality of the evidence. Indeed, and as further explained in defendants' motions to exclude plaintiffs' experts' opinions, it is plaintiffs' experts who have turned a blind eye to the overwhelming weight of the literature that is at odds with their causal conclusions, including, e.g., the entire category of cohort studies and the broad range of animal and in vitro studies that show that talc is not genotoxic and does not induce the development of ovarian cancer.[16]

In any event, the notion that an expert improperly cherry-picked because she did not cite an unpublished manuscript that was written for litigation purposes and a draft regulatory document from another country that plaintiffs think support their position is too ridiculous to merit a response. Indeed, plaintiffs' obsessive focus on the Health Canada draft report (and the unpublished meta-analysis by Mohamed Taher and others from which the report draws) highlights the fact that the real scientific literature offers no support for their speculative and unscientific theories.

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[16] (*See, e.g.*, Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts' General Causation Ops. ("Defs.' GC Mot.") at 47-66, May 7, 2019 (ECF No. 9736) (highlighting plaintiffs' experts' disregard of cohort studies and the unreliable justifications they proffered in support of their approach); Defs.' Mem. of Law in Supp. of Mot. to Exclude Expert Ops. of Ghassan Saed at 50-52, May 7, 2019 (ECF No. 9736-2) (noting that Dr. Saed failed to take account of or explain away literature that had concluded that talc is not genotoxic, contrary to the claimed results of his study).)

IV. PLAINTIFFS ATTEMPT TO TURN THE SCIENTIFIC WORLD ON ITS HEAD WITH RESPECT TO STATISTICAL SIGNIFICANCE AND THE HIERARCHY OF SCIENTIFIC EVIDENCE.

Plaintiffs' briefing repeatedly asserts that defendants' experts have somehow run afoul of scientific principles by paying heed to longstanding scientific norms concerning statistical significance and the hierarchy of evidence.[17] On both scores, plaintiffs depart from the *Reference Manual* that they otherwise embrace, instead turning to a longtime dissenter from the scientific mainstream on these issues, Dr. Kenneth Rothman, and their expert consultant, Dr. Sander Greenland.

Statistical Significance: As the *Reference Manual* explains, "[t]he two main techniques for assessing random error are statistical significance and confidence intervals."[18] Statistical significance is a statement about the likelihood that the positive association observed in a study is "the result of random error."[19] It is "an important metric to distinguish between results supporting a true association and those resulting from mere chance." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 793 (3d Cir. 2017).

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[17] (*E.g.*, Pls.' Br. at 26-30; Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude the Ops. of Defs.' Epidemiology Experts Karla Ballman, Christian Merlo, Gregory Diette, and Jonathan Borak ("Pls.' Epi. Mot.") at 13-47, May 7, 2019 (ECF No. 9737-1).)

[18] Green et al., Fed. Judicial Ctr., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence* 549, 573 (3d ed. 2011) ("Epidemiology Reference Manual").

[19] *Id.* at 575.

As the *Reference Manual* acknowledges, there is "some controversy among epidemiologists and biostatisticians about the appropriate role of significance testing."[20] Some have argued for a diminished reliance on statistical significance, while others have argued for ***greater*** reliance on and higher standards of statistical significance.[21] But nothing supports the notion that statistical significance is simply "irrelevant," as plaintiffs' experts have contended,[22] or that it should "be expunged from the lexicon of the epidemiologist,"[23] a position that the Third Circuit expressly rejected in *In re Zoloft*, 858 F.3d at 799 (concluding that an expert's method was "too far-reaching" and "understat[ed] the importance of statistical significance").[24]

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20 *Id.* at 578.

21 *E.g.*, Benjamin et al., *Redefine Statistical Significance*, 2 Nature Human Behaviour 6 (2018) (attached as Ex. A160 to Suppl. Certification of Julie L. Tersigni ("Suppl. Tersigni Cert.")) (commentary article signed by 70 authors advocating for a shift to p-value of 0.0005, which would have the effect of making it harder to establish statistical significance, citing the "growing concern over the credibility of claims of new discoveries based on 'statistical[] significan[ce]'").

22 (*See* Defs.' GC Mot. at nn.151 & 156 (identifying five examples).)

23 (Pls.' Br. at 28 (citation omitted).)

24 This Court and many others have likewise recognized the importance of statistical significance. *See, e.g., Bracco Diagnostics, Inc. v. Amersham Health, Inc.*, 627 F. Supp. 2d 384, 452 (D.N.J. 2009) (Wolfson, J.) (holding that the opinions of an expert who "testified that the 0.05 p-value test for statistical significance was not grounded in solid science" were inadmissible; the expert's statements "regarding the use of the p-value [were] not properly based upon science and [were] not reliable"); *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 892 F.3d 624, 642 (4th Cir. 2018) (affirming the exclusion of plaintiffs' expert Dr. Sonal Singh's causation opinion "because the

Plaintiffs' authorities do not support any departure from Third Circuit precedent on this issue. Their principal authority – Dr. Rothman – has been arguing that "statistical significance testing is of little value" for more than three decades.[25] He even took this position as an amicus in support of the plaintiffs in *Daubert* (although the Supreme Court's ruling notably did not even mention, much less embrace, Dr. Rothman's views on statistical significance).[26] But Dr. Rothman's view has not gained general acceptance, as the *In re Zoloft* ruling makes plain.

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plaintiffs 'failed to demonstrate that Dr. Singh's reliance on non-statistically significant "trends" is accepted in his field, that non-statistically significant findings have served as the basis for any epidemiologist's causation opinion in peer-reviewed literature, or that standards exist for controlling the technique's operation'") (citation omitted); *Burst v. Shell Oil Co.*, No. 14-109, 2015 WL 3755953, at *12 (E.D. La. June 16, 2015) (excluding expert who relied on studies that did not show statistically significant results because "such studies do not reliably support epidemiologists' general causation opinions in the context of toxic tort litigation"; "Many of the studies on which [the expert] relied did not produce statistically significant results and his reliance on them is therefore questionable.").

[25] Woolson & Kleinman, *Perspectives On Statistical Significance Testing*, 10 Ann. Rev. Pub. Health 423, 423-24 (1989) (attached as Ex. A177 to Suppl. Tersigni Cert.) (referencing Dr. Rothman's views).

[26] Br. Amici Curiae of Profs. Kenneth Rothman, Noel Weiss, James Robins, Raymond Neutra & Steven Stellman, in Supp. of Pet'rs, *Daubert v. Merrell Dow Pharm., Inc.*, No. 92-102, 1992 WL 12006438, at *3-8 (U.S. filed Dec. 2, 1992). The citations in plaintiffs' Omnibus Brief to "Rothman Amici Brief" (p. 28 n.102) and "Brief for Kenneth Rothman et al." (p. 33 n.123) are to this filing.

Nor does the recent commentary published in *Nature* by Valentin Amrhein and plaintiffs' previously disclosed expert Dr. Greenland suggest otherwise.[27] As a threshold matter, the necessary premise of the commentary, which seeks to "***Retire Statistical Significance***" (emphasis added), is that statistical significance is generally accepted and employed in the scientific community. Moreover, the Amrhein proposal expressly did "not advocat[e] a ban on *P* values, confidence intervals or other statistical measures – only that we should not treat them categorically"; nor did it "***advocat[e] for an anything goes situation, in which weak evidence suddenly becomes credible***."[28] And *Nature*'s editorial board expressly stated in the very same issue of the journal that it has ***no plans to "change how [the journal] considers statistical [significance]."***[29] Others responding to the commentary – including in *Nature* itself and in the *Journal of the American Medical Association* – strongly rejected the notion that statistical significance has no relevance out of hand.[30] Meanwhile, leading journals[31] and

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[27] Amrhein et al., *Retire Statistical Significance*, 567 Nature 305 (Mar. 21, 2019) ("Amrhein 2019") (attached as Ex. A8 to Tersigni Cert.). Dr. Greenland was disclosed as a consulting expert for plaintiffs. (Pls.' Steering Committee's Initial Designation & Disclosure of Non-Case Specific Expert Witnesses at 6 (attached as Ex. I3 to Tersigni Cert.).)

[28] Amrhein 2019 at 306 (emphasis added).

[29] *See Significant Debate*, 567 Nature 283 (Mar. 21, 2019) (attached as Ex. A132 to Tersigni Cert.).

[30] *See, e.g.*, Johnson, *Retiring Significance: Raise the Bar*, 567 Nature 461 (2019) (attached as Ex. A81 to Tersigni Cert.) (explaining that results that are

even plaintiffs' own experts[32] continue to publish articles that rely on assessments of statistical significance. In short, it simply is not true, as plaintiffs and their

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barely statistically significant often "provide evidence supporting the null hypothesis of no association" when carefully examined); Ioannidis et al., *The Importance of Predefined Rules and Prespecified Statistical Analyses: Do Not Abandon Significance*, JAMA Online (2019), https://jamanetwork.com/journals/jama/fullarticle/2730486 (attached as Ex. A79 to Tersigni Cert.) (explaining that objective pre-defined standards like statistical significance remove "leeway to manipulate the data and hack the results to claim important signals" and that without such standards, "science and policy may rely less on data and evidence and more on subjective opinions and interpretations").

[31] *See, e.g.*, King et al., *A Trial of a Triple-Drug Treatment for Lymphatic Filariasis*, 379 New England J. of Med. 1801, 1804-05, 1807 tbl. 2 (2018) (attached as Ex. A167 to Suppl. Tersigni Cert.) (conducting detailed analysis of statistical significance and concluding that the tested three-drug regimen was superior to a two-drug regimen where the former "resulted in significantly greater microfilarial clearance" at a level of "$P = 0.02$"); Wise et al., *Effect of Aclidinium Bromide on Major Cardiovascular Events and Exacerbations in High-Risk Patients With Chronic Obstructive Pulmonary Disease: The ASCENT-COPD Randomized Clinical Trial*, 321(17) JAMA 1693, 1693 (2019) (attached as Ex. A174 to Suppl. Tersigni Cert.) (finding that patients dosed with aclidinium saw a statistically significant reduced rate of pulmonary disease exacerbations, at the level of "$P < .001$" for "moderate to severe exacerbation[s]" and "$P = .006$" for "exacerbations requiring hospitalization"); Choi et al., *Risk Factors for* Elizabethkingia *Acquisition and Clinical Characteristics of Patients, South Korea*, 25(1) Emerging Infectious Diseases 42, 47-50 (2019) (attached as Ex. A162 to Suppl. Tersigni Cert.) (finding that use of mechanical ventilation among hospital patients was a risk factor for contracting *Elizabethkingia* infection, based on a statistically significant association at a level of "$P < 0.001$").

[32] *See, e.g.*, Demb et al., *Optimizing Radiation Doses for Computed Tomography Across Institutions*, 177(6) JAMA Internal Med. 810, 810, 815 tbl. 2 (2017) (attached as Ex. A163 to Suppl. Tersigni Cert.) (article co-authored by plaintiffs' expert Dr. Rebecca Smith-Bindman concluding that educational meetings were effective in lowering radiation doses where "*P* values represent[ing] test for change in means" before and after intervention were highly statistically significant at "<.001"); Mason et al., *Vitamin D_3 Supplementation During Weight*

experts contend, that statistical significance is "irrelevant"[33] or that considering statistical significance renders an expert's opinions unreliable.

Hierarchy of Evidence: It is a "fundamental principle of evidence-based medicine" that scientific evidence "is hierarchical."[34] As detailed in defendants' general causation brief, this hierarchy places randomized clinical trials at the top, followed by observational studies and case reports, case series and other

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Loss: A Double-Blind Randomized Controlled Trial, 99 Am. J. Clin. Nutr. 1015, 1015 (2014) (attached as Ex. A169 to Suppl. Tersigni Cert.) (article co-authored by plaintiffs' expert Dr. Anne McTiernan concluding that Vitamin D_3 supplementation did not increase weight loss because of a lack of statistically significant results in relevant measurements – "all $P > 0.05$"); Moorman et al., *A Prospective Study of Weight Gain After Premenopausal Hysterectomy*, 18 J. of Women's Health 699, 702 (2009) (attached as Ex. A170 to Suppl. Tersigni Cert.) (finding an association between hysterectomies and weight gain where a statistical "model fully adjusted for all potential confounders . . . showed a difference in weight gain of 0.89 kg (~2.0 pounds, [P] = 0.04)" between test and control groups); Tisminetzky et al., *Magnitude and Impact of Multiple Chronic Conditions with Advancing Age in Older Adults Hospitalized with Acute Myocardial Infarction*, 272 Int'l J. of Cardiology 341, 342–44, 343 tbl. 2 (2018) (attached as Ex. A172 to Suppl. Tersigni Cert.) (article co-authored by plaintiffs' expert Sonal Singh finding relationships between treatment decisions and patient age, with differences in surgical decisions and certain medication decisions "[s]ignificant at [P] ≤ 0.001").

[33] Plaintiffs contend in their brief addressing defendants' epidemiology experts that the experts place too much emphasis on statistical significance. (Pls.' Epi. Mot. at 17-28.) That argument mischaracterizes defendants' experts' approach, as defendants elaborate in their opposition to that brief. (Defs.' Mem. of Law in Opp'n to Pls.' Mot. to Exclude the Ops. of Defs.' Epidemiology Experts at 23-31 (filed herewith and incorporated herein).)

[34] Wong et al., Fed. Judicial Ctr., *Reference Guide on Medical Testimony, in Reference Manual on Scientific Evidence* 687, 723 (3d ed. 2011) ("Medical Testimony Reference Manual") (attached as Ex. A175 to Suppl. Tersigni Cert.).

unsystematic evidence.[35] Within the tier of observational studies, cohort studies are generally ranked above case-control studies because their prospective ascertainment of exposure generally reduces or eliminates the effects of bias.[36]

Plaintiffs assert that observational studies should "not [be evaluated] on the basis of any co-called 'hierarchies' or 'pyramids' that presume one study design

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[35] (Defs.' GC Mot. at 9-12.) *See also* Medical Testimony Reference Manual at 723-24. As the *Reference Manual* notes, well-conducted systematic reviews such as meta-analyses can provide a higher level of evidence than single clinical trials or observational studies. *See id.*

[36] World Cancer Res. Fund & Am. Inst. for Cancer Res., *Continuous Update Project Expert Report: Judging the Evidence* at 7 (2018) (attached as Ex. A153 to Tersigni Cert.) (panel Dr. McTiernan serves on explaining that "[t]he hierarchy of epidemiological evidence places cohort studies above case-control studies" and that "[c]ohort studies are likely to be the main source of evidence" due in part to their prospective design); Langseth et al., *Perineal Use of Talc and Risk of Ovarian Cancer*, 62 J. Epidemiology & Cmty. Health 358, 358 (2008) (attached as Ex. A88 to Tersigni Cert.) (study co-written by Dr. Siemiatycki explaining that a talc cohort study was "arguably the strongest study because of its partly prospective ascertainment of exposure" and conversely, that "the influence of . . . recall bias cannot be ruled out" in case-control studies) (emphasis omitted); *Carl v. Johnson & Johnson*, Nos. ATL-L-6546-14, ATL-L-6540-14, 2016 WL 4580145, at *12, *19 (N.J. Super. Ct. Law Div. Sept. 2, 2016) (case-control studies "are considered less reliable than a prospective cohort study"), *appeal pending*; *Planned Parenthood Fed'n of Am. v. Ashcroft*, 320 F. Supp. 2d 957, 985 (N.D. Cal. 2004) (recognizing that "[r]esearch methodology is evaluated on a hierarchy," with prospective studies ranking above retrospective studies), *aff'd sub nom. Planned Parenthood Fed'n of Am., Inc. v. Gonzales*, 435 F.3d 1163 (9th Cir. 2006), *rev'd on other grounds sub nom. Gonzales v. Carhart*, 550 U.S. 124 (2007); *see also* Epidemiology Reference Manual at 557-60 (not expressly addressing relative strengths of the two designs but noting that there are a "number of potential problems with case-control studies," referring to a subsequent section addressing bias).

generally had more value than another generally."[37] But they again rely exclusively on Dr. Rothman for this proposition,[38] and Dr. Rothman's limited observations about what he describes as "persistent research misconceptions" do not sweep as broadly as plaintiffs contend.[39] Rather, Rothman's point is only that researchers should take a holistic approach that considers the quality of study design and all available data – and that "discrepancies between cohort studies and case-control studies should not be explained away superficially by a presumed validity advantage for cohort studies over case-control studies."[40] A reminder that a "presumed validity advantage" may be rebutted is not an attack on the underlying presumption itself – and no defense expert has premised her or his opinion solely on the presumption that cohort studies occupy a higher position on the hierarchy of evidence than case-control studies. To the contrary, all three of defendants' experts consider the full array of observational studies in reaching their conclusions.[41] Accordingly, plaintiffs' attack on the "fundamental principle" of the hierarchy of scientific evidence is unfounded.

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37 (Pls.' Br. at 31.)

38 (*See id.* at 31 & n.115.)

39 *See* Rothman, *Six Persistent Research Misconceptions*, 29 J. Gen'l Internal Med. 1060 (2014) (attached as Ex. I to Pls.' Br.).

40 *Id.* at 1061.

41 (*See* Expert Report of Karla Ballman, Ph.D. at 22-35, Feb. 25, 2019 (attached as Ex. C25 to Tersigni Cert.); Expert Report of Gregory Diette, M.D., M.H.S. at 8-19, Feb. 25, 2019 (attached as Ex. C18 to Tersigni Cert.); Expert

CONCLUSION

For the foregoing reasons, and for the additional reasons set forth in defendants' oppositions to plaintiffs' motions to exclude defendants' experts, the Court should deny plaintiffs' motions.

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Respectfully submitted,

/s/ Susan M. Sharko

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(cont'd from previous page)
Report of Christian Merlo, M.D., M.P.H. at 13-35, Feb. 25, 2019 (attached as Ex. C13 to Tersigni Cert.).)